II. REMARKS

Claims 1, 4, 7-11 and 16-33 were examined and stand variously rejected. Claims 7 to 11 have previously been withdrawn from consideration as a result of a requirement for restriction. By this Amendment, claims 16 - 18, 20 - 22, 25 – 27 and 31 - 33 have been canceled without prejudice or disclaimer. Claims 1, 4, 19, 24 and 29 have been amended. New claims 34-37 have been added.

Applicants' cancellation of claims and the amendment of the claims as previously presented are made without prejudice to Applicants' right to pursue the same or similar claims in a related application. The cancellation of these claims and the amendment of claims 1, 4, 19, 24 and 29 are not intended to be a dedication to the public of the subject matter of the claims as previously presented.

The claim amendments do not raise an issue of new matter. Support for the amendments to the claims and the addition of new claims is found in Example 4, on page 34, line 13 to page 36, line 10; page 9, line 21 through page 10, line 29; and page 14, line 1 through page 26, line 5.

Entry of these amendments and new claims is respectfully requested.

In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the rejections is respectfully requested. After amending the claims as set forth above, claims 1, 4, 19, 23, 24, 28-30 and 34-37 are presented for examination.

Interview Summary

Applicants and their representative thank the Office for the courtesy extended to them during the November 17, 2008 telephonic interview. The interview was helpful in clarifying the issues and presenting the currently amended claims.

Applicants agree with the Office's Statement of Interview issued November 18, 2008. The Office summarized that the interview discussion was limited to the enablement rejection of the independent claims and possible amendment of the claims to clarify that the method is one which analyzes the nucleotide sequence of the ERCC1 gene to determine the nucleotides present at codon 118. No exhibits were presented or discussed and no agreement was reached.

Election/Restrictions

The Office acknowledged Applicants' withdrawal of claims 7-11 from consideration as being drawn to a nonelected invention and that election of Group I was made without traverse on September 9, 2007. The Office also withdrew claims 29-33 as being allegedly directed to the subject matter of the non-elected invention of Group II. Group II is drawn to a method for treating neurotoxicity associated with cancer [chemotherapy] by administering a Cox-2 inhibitor. The Office alleges that the claims do not recite an active process step for selecting a patient for therapy and thus does not limit the claims to methods of selecting therapy by assaying for the genotype at codon 118 of the ERCC1 gene, i.e. the subject matter of elected Group I.

Applicants respectfully traverse the withdrawal of claims 29-33 based on being directed to the subject matter of Group II. Claim 29 has been amended to recite the steps of screening and identifying the patient for the same therapy as, for example, claims 1 and 19. In view of the amendment to claim 29 and the cancellation of claims 31 and 33, reconsideration and examination of claims 29, 30 and 32, is respectfully requested.

35 USC § 112, 1st Paragraph

Claims 1, 4 and 16-28 stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that the specification only enables claims to methods for predicting the survival of a human patient having metastatic colon cancer, the method comprising: i) obtaining a nucleic acid sample from colon cancer tissue or colon cancer cells of a human patient having metastatic colon cancer or colon cancer cells of a human patient having metastatic colon cancer and treated with 5-fluoropyrimidine (5-FU) and oxaliplatin, wherein the nucleic acid sample comprises ERCC1 nucleic acids; ii) analyzing the sequence of the ERCC1 nucleic acids to determine the nucleotides present at codon 118; and iii) determining that the patient will have a longer survival following treatment with 5-FU and oxaliplatin if the patient has a C/C genotype at codon 118 of ERCC1, as compared to patients having a C/T or T/T genotype at codon 118 of ERCC1, allegedly does not reasonable provide enablement for methods which select any therapeutic regimen in any subject having any type of cancer by assaying for any polymorphism or genotype of the ERCC1 gene or any other gene. The Office alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Prior to responding to the substance of the rejection, Applicants note that the independent claims (and therefore the claims that depend upon them) have been amended to recite that the nucleotide sequence at codon 118 of the ERCC1 gene present in a patient cell or tissue sample is assayed. The amended claims therefore do not encompass methods of indirectly detecting the genotype at codon 118, i.e. by assaying gene expression levels of ERCC1.

Applicants also have amended the therapy element of the claims to the administration of 5-Fluorouracil and oxaliplatin. However, Applicants respectfully traverse and note that the specification, in combination with the level of skill and

knowledge in the art at the time the application was filed enable methods for screening any cell or tissue for the genotype of interest for use in an appropriate therapy.

With respect to the tissue or cell sample, Applicants direct the Office to page 10, lines 12 to 22 and page 25, lines 21 to 25 of the application which notes that the methods of the invention can utilize any cell or tissue sample to determine the genotype at codon 118 of the ERCC1 gene. In support of this position, Applicants direct the Office to the technical article cited as Stoehlmacher, et al. (2004) "A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer" British J. of Cancer, Vol. **91**, pages 344-354. A copy of this publication is attached to the Supplemental Information Disclosure Statement (IDS) concurrently filed with this reply. On page 345 of the article, the authors (which includes the named coinventors) note that the polymorphisms tested (which includes the claimed ERCC1 118 codon) was accomplished through PCR analysis of whole blood samples isolated from the patients. Thus, any tissue having genomic DNA is a suitable cell or tissue sample for the claimed methods. Removal of this ground for rejection is respectfully requested.

Applicants draw the Examiner's attention to the post-filing technical references (Ref. Nos. D28-D46) cited in the attached PTO SB/08 describing correlation between ERCC1 gene sequence at codon 118 with various therapeutic outcomes and various treatments.

In view of the preceding amendments and remarks, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. §112, first paragraph is respectfully requested.

Double Patenting

Claims 1, 4 and 16 to 28 stand provisionally rejected on the ground of non-statutory double patenting as allegedly unpatentable over claim 1 of co-pending U.S. Serial No. 11/173,889. The cancellation of claim 1 in U.S. Serial No. 11/173,889 has removed this ground for rejection. Reconsideration is respectfully requested.

35 USC § 112 Second Paragraph

Claims 19 to 28 stand rejected as allegedly unpatentable for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. The Office alleged that the claims were indefinite in use of the relative terms "longer" in claims 19 to 28 and "less likely" in claims 24 to 28, without a standard for ascertaining the requisite degree.

Without conceding the correctness of the Office's position and in a sincere effort to advance examination, Applicants have amended the claims to note that the standard for the term "longer" in claims 19 to 28 are patients not possessing the stated genotype but which are receiving the same treatment. In addition, the use of the qualifier "less" in claims 24-28 has been deleted. Support for the amendments is found in the specification on page 36, lines 1 to 5.

In view of the preceding amendments and remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph is respectfully requested.

Priority

The Office questioned the priority claim to U.S. provisional applications 60/400,276; 60/400,250 or 60/400,249. The Office alleged that the claims are only entitled to a priority date of July 31, 2003 (the PCT filing date) on the ground that the

provisional application 60/440,253 filed on July 13, 2002 does not support the broader concepts encompassed by the claims such as for selecting a therapy comprising any combination of fluoropyrimidine and platinum compound, or predicting likelihood or less likelihood of longer survival following treatment with any combination of a fluoropyrimidine and platinum compound, etc.

Applicants respectfully traverse and note that the priority applications were all filed on the same date, i.e., July 31, 2002. The amended and withdrawn claims (all still currently pending) are supported in the July 31, 2002 filings. In view of the amendments to the claims, Applicants respectfully request adjustment of the Office's statement regarding the priority claim of the currently pending claims.

35 USC § 103

Claims 1, 16-22 and 24-27 were rejected for allegedly being obvious over the disclosure of Park et al. (Proceeding of the American Association for Cancer Research, March 2002, 43:321, Abstract 1516 (cited in the IDS of May 15, 2008). Briefly, the Office alleged that Park et al. teaches detecting the presence of the C or T polymorphism at codon 118 of the ERCC1 gene in intratumoral tissue samples from human subjects having metastatic colorectal cancer and treated with 5-FU/oxaliplatin. Park et al. also was cited for teaching that increased ERCC1 mRNA levels are directly related to clinical resistance to platinum chemotherapy and the absence of the ERCC1 C allele was associated with higher ERCC1 mRNA levels.

Claims 4, 23, and 28 were separately rejected for allegedly being obvious over the combined teachings of Park et al. (above) in view of Culy (Drugs, October 2000 **60(4)**:895-924). The Office relied on the teachings of Park et al. as outlined above and added Culy for the teaching that it was conventional in the art at the time the invention was made to also treat metastatic colorectal cancer patients receiving 5-FU/oxaliplatin therapy with radiation therapy.

Applicants respectfully traverse. Attached to this Reply is a Declaration Under 37 C.F.R. § 1.132 by the coinventors stating that the work described in Park et al. is their own. The authors of the Abstract not named as coinventors worked under the direction and supervision of the named inventors and therefore were not named as coinventors. Accordingly, the Abstract is a publication of the inventors published less than one year prior to the effective filing date (July 13, 2002) and therefore cannot be cited against the claims under 35 U.S.C. § 103. Without the teachings of Park et al., the secondary reference Culy, also fails to teach or suggest the claimed invention.

In view of the attached Declaration and the preceding remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103, is respectfully requested.

Supplemental Information Disclosure Statement

Applicants gratefully acknowledge the initialed SB/08 Forms attached to the outstanding Office Action. Also attached to this Reply is a Supplemental Information Disclosure Statement listing references for consideration and entry into the application file. Applicants respectfully request that the Office acknowledge same by initializing the SB/08 document and returning the initialed copy to Applicants' attorney in the next correspondence.

III. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed

herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 5, 2009

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